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ORIGINAL ARTICLE

Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries

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Abstract Nasal high-frequency oscillation ventilation (nHFOV) is a non-invasive ventilation mode that applies an oscillatory pressure waveform to the airways using a nasal interface. nHFOV has been shown to facilitate carbon dioxide expiration, but little is known about its use in neonates. In a questionnaire-based survey, we assessed nHFOV use in neonatal intensive care units (NICUs) in Austria, Switzerland, Germany, the Netherlands, and Sweden. Questions included indications for nHFOV, equipment used, ventilator settings, and observed side effects. Of the clinical directors of 186 NICUs contacted, 172 (92 %) participated. Among those responding, 30/172 (17 %) used nHFOV, most frequently in premature infants <1500 g (27/30) for the indication nasal continuous positive airway pressure (nCPAP) failure (27/30). Binasal prongs (22/30) were the most common interfaces. The median (range) mean airway pressure when starting nHFOV was 8 (6–12) cm H_2O, and the maximum mean airway pressure was 10 (7–18) cm H_2O. The nHFOV frequency was 10 (6–13) Hz. Abdominal distension (11/30), upper airway obstruction due to secretions (8/30), and highly viscous secretions (7/30) were the most common nHFOV side effects.

Conclusion: In a number of European NICUs, clinicians use nHFOV. The present survey identified differences in nHFOV equipment, indications, and settings. Controlled clinical trials are needed to investigate the efficacy and side effects of nHFOV in neonates.

Keywords High-frequency oscillation · Non-invasive ventilation · Continuous positive airway pressure · Side effects · Neonate · Survey

Abbreviations

BPD	Bronchopulmonary dysplasia
HFOV	High-frequency oscillation ventilation
nCPAP	Nasal continuous positive airway pressure
nHFOV	Nasal high-frequency oscillation ventilation
NICU	Neonatal intensive care unit
nIPPV	Nasal intermittent positive pressure ventilation
P_{mean}	Mean pressure
RDS	Respiratory distress syndrome
VLBW	Very low birth weight infant

Introduction

Respiratory distress syndrome (RDS) often requires intubation and mechanical ventilation [31]. However, endotracheal ventilation has been associated with lung injury [20] and the development of bronchopulmonary dysplasia (BPD) [21]. Although modern clinical strategies using nasal continuous positive airway pressure (nCPAP) and early surfactant application have been shown to reduce endotracheal ventilation and BPD in very preterm infants [30, 14], 33–83 % of nCPAP

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patients in randomized controlled trials still required intubation at some point during their clinical course [18, 25]. Some of these infants fail nCPAP because nCPAP does not necessarily improve alveolar ventilation or CO_2 elimination [2]. Consequently, non-invasive ventilation modes that actively support gas exchange may be more efficient in this and similar clinical settings. Nasal high-frequency oscillation ventilation (nHFOV) is a non-invasive ventilation mode, in which an oscillatory pressure waveform is applied to the airways to improve alveolar recruitment and CO_2 removal [7, 23]. This method is therefore regarded as a possible improvement over nCPAP and an alternative to other non-invasive ventilation modes, such as nasal intermittent positive pressure ventilation (nIPPV) [11]. Unlike nIPPV, nHFOV does not require synchronization with the patient's breathing [2, 26]. In a newborn mannequin study, nHFOV was superior to nIPPV in eliminating CO_2 from the lungs [23]. Clinical crossover studies comparing nCPAP with nHFOV showed that nHFOV decreased pCO_2 in neonates with respiratory insufficiency [32] and in very low birth weight infants (VLBWs) stable on nCPAP [4]. Another small observational study demonstrated the feasibility of nHFOV use immediately after extubation in difficult-to-wean preterm infants [6].

Although nHFOV appears to be a promising non-invasive ventilation mode for neonates, few preliminary clinical studies have been performed to date, involving different indications, equipment, and nHFOV settings. Some neonatologists, however, already use nHFOV in the clinical setting. This study was therefore designed to obtain information about the prevalence and clinical application of nHFOV in neonatal intensive care units (NICUs) in five European countries.

Materials and methods

Questionnaire

A questionnaire-based survey about the use of neonatal nHFOV in Austria, Switzerland, Germany, the Netherlands, and Sweden was conducted between June 2013 and February 2014. For this purpose, a questionnaire was developed and pretested by three neonatal consultants in our department. The questionnaire started with three questions about the characteristics of the institution (Table 1), followed by questions about the use of nHFOV in neonates. Those who stated that they used nHFOV were asked to complete the second part of the questionnaire, which was divided into four sections, addressing (1) equipment used, (2) indications for nHFOV, (3) ventilator settings, and (4) side effects. Most questions were multiple choice. Where appropriate, the questionnaire explicitly asked for additional information, e.g., specifying "other" side effects. The entire questionnaire can be viewed in Online Resource 1.

Protocol

The questionnaire was sent by e-mail to the clinical directors of NICUs who provide the highest level of care in their country, corresponding to American Academy of Pediatrics level III [1]. To identify these units in Germany, we based our search on a list of German level I neonatal units (equivalent to level III in the USA) used in a previous survey [5]. Eligible NICUs in Austria and Switzerland were identified by C.B., and units in Sweden and the Netherlands were identified by K.B. and I.R., respectively. All information was verified by a thorough internet search and updated as necessary. Clinical directors were trusted to answer the questionnaire in person or to delegate this task appropriately, and to represent the whole NICU team's experience with nHFOV accurately. The responses to the survey were closely monitored. Once the feedback to the first e-mail abated, a reminder questionnaire was e-mailed to those who did not respond, followed by posted mail and contact by telephone, if necessary. In Sweden, the initial e-mail questionnaire was directly followed up by a telephone contact.

Statistical methods

Categorical data are described in absolute numbers and percentages and compared between countries using the chi-square test. Quantitative data are reported as median and range and compared by the Mann-Whitney *U* test or the Kruskal-Wallis test, as appropriate. Statistical evaluations were performed using SPSS software (SPSS Statistics version 22, IBM Corporation, USA). A p value <0.05 was defined as statistically significant.

Results

Of the clinical directors of 186 NICUs contacted, 105 (56.5 %) responded to the e-mail questionnaire, another 35 (19 %) to the mailed questionnaire, and another 32 (17 %) to direct telephone contact. One (0.5 %) declined to participate in the survey. The remaining 13 (7 %) did not provide the information requested. The overall participation rate was 92 %. It was 100 % in Austria, Switzerland, and Sweden; 91 % in Germany; and 80 % in the Netherlands. Of the participating institutions, 46 had to be contacted once more to complete or verify answers. Apart from some missing details about nHFOV settings and humidifier use, as reported below, all datasets were complete.

The characteristics of the 172 NICUs that participated in the survey are shown in Table 1. The distribution of NICUs in relation to the number of inborn VLBWs was skewed, with more than half of the units reporting ≤50 VLBWs per year (Fig. 1). Although the units differed between the five countries with regard to their numbers of inborn neonates, inborn

Table 1 Participating NICUs in the five countries, median (range) operating numbers, and nHFOV use

	Austria $n=8$	Switzerland $n=11$	Germany $n=126$	Netherlands $n=8$	Sweden $n=19$	p value
Inborn neonates	1850 (1200–3496)	1400 (0–4800)	1300 (800–4713)	1400 (2000–2500)	2846 (1806–10,823)	<0.001
Inborn VLBWs	63 (28–215)	80 (0–140)	50 (10–209)	188 (100–250)	19 (8–94)	<0.001
Ventilator beds	12 (6–22)	8 (2–23)	10 (4–28)	18 (12–33)	3 (1–14)	<0.001
nHFOV use	1 (13 %)	2 (18 %)	25 (20 %)	1 (13 %)	1 (5 %)	0.742

Differences between the five countries were analyzed by the Kruskal-Wallis and chi-square tests

VLBWs, and ventilator beds (Table 1), there were no statistically significant differences in the incidence of nHFOV application. The median (range) number of ventilator beds was significantly greater in NICUs that used nHFOV (12 (1–28) vs. 8 (1–33), $p=0.019$). Altogether, 30 (17 %) of the responding neonatologists in 172 units confirmed their use of nHFOV, employing various types of equipment.

Equipment

The ventilators used most commonly for nHFOV were the Babylog 8000 (Dräger Medical GmbH, Germany), the Stephanie (Fritz Stephan GmbH, Germany), and the Leoni Plus (Heinen + Löwenstein GmbH, Germany) (Fig. 2). Physicians in five NICUs each used a combination of two or more of the ventilators specified in Fig. 2, and in one unit, they relied on either the Babylog 8000 or the 3100A (CareFusion Corporation, USA). Among the responders who applied nHFOV, 18 of 30 (60 %) used humidifiers supplied by Fisher & Paykel Healthcare, New Zealand, but only 6 specified the exact humidifier type (FP 700, MR 850, MR850 AGU, or MR 730). Seven (23 %) used the Stephanie ventilator and its integrated humidifier (Gründler Medical, Germany), two (7 %) used Gründler medical humidifiers without further specification, and three (10 %) did not indicate the humidifiers they used. Binasal prongs were the most common interface for nHFOV, used in 22 of 30 (73 %) NICUs, followed by nasopharyngeal tubes (Table 2).

Indications for nHFOV

Responses to questions about nHFOV indications are presented in Table 2. nHFOV was most frequently used in preterm infants weighing <1500 g (27/30). The most common indication was nCPAP failure (27/30), as defined by the clinicians in charge. Neonatologists in 15 of the 30 NICUs (50 %) applied nHFOV immediately after extubation without trying nCPAP first. Most of them extubated both from conventional ventilation and high-frequency oscillation ventilation (HFOV) directly to nHFOV. While physicians in 4 of the 30 NICUs used nHFOV regularly, the others had tried it only occasionally (12/30) or rarely (14/30).

Ventilator settings

The median and range of the reported nHFOV frequency, the mean pressure (P_{mean}) when starting nHFOV, the maximum P_{mean}, the P_{mean} before switching to nCPAP, and the maximum amplitude are shown in Table 3. A broad range of settings was reported for each nHFOV parameter. Several of the NICUs provided incomplete datasets, especially for maximum pressure and amplitude. As the operator could not adjust the ventilator flow in the majority of ventilators used, this item was not further analyzed.

Side effects

Table 2 shows that abdominal distension (11/30), upper airway obstruction due to secretions (8/30), and highly viscous secretions (7/30) were the most common side effects reported more frequently during nHFOV than during nCPAP. Other

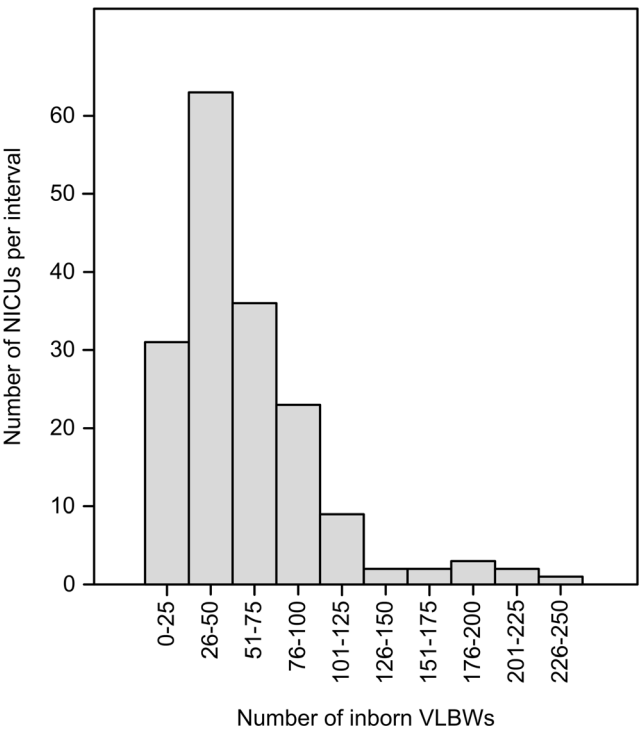

Fig. 1 Histogram of all participating NICUs in relation to their number of inborn VLBWs per year

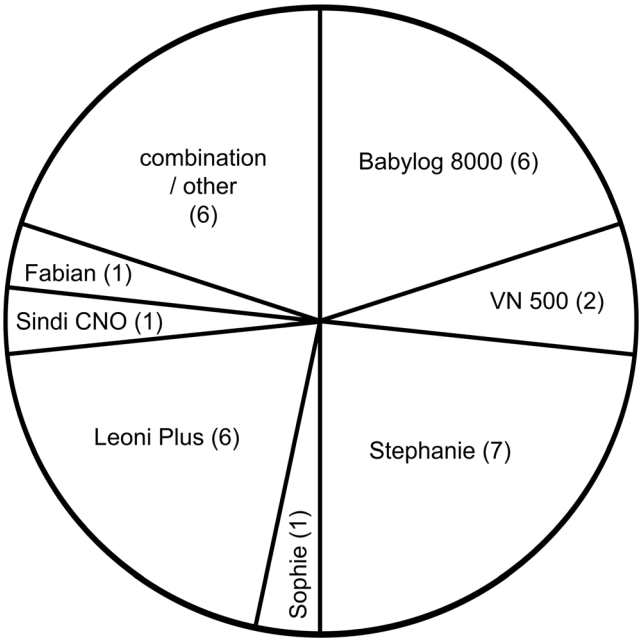

Fig. 2 Ventilators employed by the NICUs using nHFOV: Babylog 8000, VN 500 (Dräger Medical GmbH, Germany); Stephanie, Sophie (Fritz Stephan GmbH, Germany); Leoni Plus, Sindi CNO (Heinen + Löwenstein GmbH, Germany); Fabian HFO (Acutronic Medical Systems, Switzerland). Absolute numbers of NICUs are in *brackets*

side effects reported by responders in single NICUs included strong agitation and pneumothorax. There was no association between side effects and particular equipment used to deliver nHFOV.

Discussion

This survey in five European countries showed that neonatologists in 30 (17 %) of 172 NICUs had clinical experience with nHFOV, although most of them used nHFOV occasionally or rarely. The responses of nHFOV users revealed that they used various types of equipment for various indications and with various nHFOV settings. Abdominal distention and upper airway obstruction due to viscous secretions were the most frequently reported side effects of nHFOV use.

With an overall response rate of 92 %, participation was better than in previous surveys investigating respiratory support [29, 17]. The considerable differences in the unit baseline characteristics between the five countries may be due to varying degrees of regionalization of neonatal care [34], to differences in national guidelines defining level III units in Europe [33], and/or to individual NICUs with special features (e.g., a highly specialized referral center in Switzerland without an obstetrics service). Despite this heterogeneity, the responses to the survey represent current clinical practice in NICUs providing the highest level of care in these five countries.

Table 2 nHFOV interfaces, indications, and side effects (answers from the NICUs with experience using nHFOV (n=30))

	Number (%)
Which interface(s) for nHFOV do you use?	
Binasal prongs	22 (73)
Single nasopharyngeal tube	19 (63)
Nose mask	5 (17)
Oronasal mask	3 (10)
Which indication(s) for nHFOV do you accept?	
Nasal CPAP failure	27 (90)
Immediately after extubation	15 (50)
Hypercapnia	5 (17)
Primary treatment of RDS	3 (10)
In your department, you extubate	
From endotracheal HFOV to nHFOV	14 (47)
From conventional ventilation to nHFOV	12 (40)
Which infants do you treat with nHFOV?	
Premature infants <1500 g	27 (90)
Premature infants >1500 g	13 (43)
Term babies	8 (27)
How often do you use nHFOV?	
Rarely	14 (47)
Occasionally	12 (40)
Regularly	4 (13)
Which specific side effects did you observe more frequently during nHFOV than during nasal CPAP?	
Abdominal distension	11 (37)
Upper airway obstruction due to secretions	8 (27)
Thick, almost solid secretions	7 (23)
Leakage around the prongs	1 (3)
Strong agitation	1 (3)
Pneumothorax	1 (3)
Ventilator dysfunction	1 (3)

Equipment

The large variety of ventilators and humidifiers used for nHFOV probably reflects the technology available on site (Fig. 2). Among the ventilators used, only the Sindi CNO has been formally approved for neonatal nHFOV by the

Table 3 Median (range) ventilator settings during nHFOV and number of NICUs that provided data

	Ventilator settings	Number
Frequency	10 (6–13) min^{-1}	27
P_{mean} when starting nHFOV	8 (6–12) cm H_2O	27
P_{mean} maximum	10 (7–18) cm H_2O	23
P_{mean} before weaning to CPAP	7.5 (5–15) cm H_2O	20
Amplitude maximum	20 (2–70) cm H_2O	13

manufacturer. Incomplete reporting of the specific humidifier type suggests that these devices are regarded as an inherent and invariable part of the ventilator circuit. The reported preference of binasal prong interfaces for nHFOV was probably due to previous findings with nCPAP. These studies showed that binasal prongs had a lower resistance than nasopharyngeal tubes [10], that binasal prongs may improve oxygenation by reducing nose leaks [16], and that these prongs were more effective in preventing re-intubation [9]. However, although the feasibility of binasal prong HFOV has been demonstrated in bench studies [7, 8], all neonatal studies to date have utilized nasopharyngeal tube interfaces for nHFOV [32, 4, 6]. This may be one reason why nasopharyngeal tubes were the second most popular interface for nHFOV. Moreover, the proximity of the nasopharyngeal tube to the larynx and the orientation of the tube ending towards the vocal cords is a theoretical advantage [19], as binasal prongs and masks employ the whole nasopharynx as a resonance body that may dampen the transmission of the oscillations [12]. Nasal and oronasal masks were the least popular interfaces, possibly because of difficulties in obtaining reliable seals.

Indications for nHFOV

There was no clear consensus about nHFOV indications among those units using it. As expected, most neonatologists applied nHFOV only occasionally or rarely in individual patients as "second-line" treatment after failure of nCPAP [32, 19]. However, some also reported using nHFOV to stabilize infants directly after extubation [6]. Only a few used nHFOV in the primary treatment of RDS or other hypercapnic respiratory failure, which must be regarded as experimental. In most institutions, nHFOV was reserved for preterm infants <1500 g. These patients may benefit most from avoidance of endotracheal ventilation because they have the highest risk of developing BPD [31]. In some NICUs, nHFOV was also applied in preterm infants >1500 g and in term babies. Although we are not aware of any nHFOV studies targeting mature infants, one pilot randomized controlled trial compared nasal high-frequency percussive ventilation, which shares some characteristics with nHFOV, with nCPAP in term babies with transient tachypnea of the newborn. This trial found that nasal high-frequency percussive ventilation reduced the duration of respiratory distress [13].

Ventilator settings

The median nHFOV frequency was 10 Hz, in agreement with previous clinical studies [32, 4, 6], although a large range between 6 and 13 Hz was reported. The reported starting P_{mean} of 8 (6–12) cm H_2O and the maximum P_{mean} of 10 (7–18) cm H_2O during nHFOV are probably higher than the corresponding nCPAP levels accepted in the same units. Although our survey did not ask about the maximum nCPAP level, a previous survey of neonatal nCPAP in Germany showed that most institutions utilized a median (range) starting level of no more than 4 (3–7) cm H_2O and a maximum nCPAP of 6.5 (4–10) cm H_2O [29]. During nHFOV, most clinicians would reduce the maximum P_{mean} to a lower level before changing to nCPAP, which also indicates that they accept a higher P_{mean} during nHFOV than during nCPAP. The observed clinical benefits of nHFOV may therefore be due to the higher pressure, not necessarily to the oscillations. To date, however, the ideal P_{mean} during nHFOV has not been determined. While optimal lung recruitment during endotracheal HFOV can be achieved in a recruitment maneuver by observing changes in oxygenation in response to incremental pressure changes [22], variable nose and mouth leaks may reduce pressure transmission and oxygenation when using nasal interfaces [16]. Choosing higher pressure levels can be dangerous in the presence of variable leaks [2]. The maximum nHFOV amplitude of the oscillations was reported to be 20 (2–70) cm H_2O. Oscillatory pressure amplitudes of 2 cm H_2O are smaller than those observed with bubble CPAP, which are about 4 cm H_2O [27]. Considerably higher amplitudes of up to 60 cm H_2O have been used previously [4, 32], and a recent bench study of neonatal nHFOV showed that the quadratic relationship between oscillation amplitude and the delivered nHFOV tidal volume plateaued at amplitudes greater than 65 cm H_2O when the frequency was 10 Hz [8]. However, the numbers of patients in the abovementioned clinical trials were far too small to establish the safety of such high nHFOV pressures and amplitudes.

Side effects

As nHFOV is similar to nCPAP with superimposed pressure oscillations, all known side effects of nCPAP may also occur during nHFOV [6]. This survey was the first study to document "typical" nHFOV side effects, which occurred more frequently during nHFOV than during nCPAP. Highly viscous secretions, upper airway obstruction due to secretions, and abdominal distention were classified as typical nHFOV side effects by 23, 27, and 36 %, respectively, of the clinicians using nHFOV. The higher mean pressures used during nHFOV than during nCPAP may account for abdominal distention and for some of the less common side effects (e.g., pneumothorax). Thick secretions with and without upper airway obstruction may be related to unsolved technical problems with the heating and humidification of the breathing gas during nHFOV. Bench studies have shown that humidifier performance may be impaired during invasive HFOV [24] and may depend on HFOV settings [3]. Moreover, high leak flows through nose and mouth leaks may heavily desiccate the nasopharynx during nHFOV, as previously described for

nCPAP [15, 28], and this effect may be augmented by the energy of the pressure oscillations.

Implications of the survey

Since these data originate from a survey, the answers should be interpreted with caution, as they merely reflect individual clinicians' experiences and preferences. The large variety of equipment used indicates that most neonatologists would be able to utilize nHFOV with available equipment, but no particular device can be recommended. The reported median settings (frequency 10 Hz, P_{mean} 8 cm H_2O when starting nHFOV, maximum amplitude 20 cm H_2O) seem reasonable but await verification in clinical trials. Concerns about safety remain, especially when using high nHFOV pressures and amplitudes, and mainly relate to pneumothorax. Apart from using the lowest efficient P_{mean} and amplitude, nursing care during nHFOV should aim to prevent airway obstruction by viscous secretions and to reduce abdominal distention. Finally, deciding when to use nHFOV poses great difficulties. The possible benefits of nHFOV need to be cautiously balanced against its risks. At this time, we believe that the limited evidence available only supports the use of nHFOV as a second-line treatment in individual patients, either for nCPAP failure or after extubation in difficult-to-wean infants. The use of nHFOV in the primary treatment of RDS should be assessed in randomized controlled trials. Ventilators and humidifiers should be optimized for use with nHFOV. Future clinical trials must test different types of equipment and nHFOV settings, as well as compare clinical outcomes of nHFOV with nCPAP, nIPPV, and synchronized nIPPV for different clinical indications and in different gestational age groups. The results of the present survey can facilitate the design of such trials.

This study had several limitations. First, the relatively small number of NICUs in which nHFOV was used (n=30) limits the statistical power of the survey and increases the risk of a type II error to detect side effects. Second, there may have been a selection bias due to arbitrary selection of the participating countries. Third, a reporting bias due to retrospective assessment may have influenced the survey results, such as a possible underreporting of the side effects of nHFOV. Fourth, the questionnaire itself contained items that left room for interpretation by the responders (e.g., the indication "nCPAP failure"), and some topics of interest were not covered (e.g., success rates of nHFOV and duration of treatment).

Conclusions

The present survey in five European countries showed that neonatologists in 17 % of 172 European NICUs used nHFOV for various indications, with various types of equipment and nHFOV settings. Upper airway obstruction due to highly viscous secretions and abdominal distention were reported to be the most frequent side effects of nHFOV. Despite the absence of clinical data about efficacy and safety, the results of this survey indicate that nHFOV is increasingly utilized in clinical practice. New studies are therefore urgently needed to define the role of nHFOV in neonates.

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Ethical standards This manuscript does not contain clinical studies or patient data.

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